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Pain control and functional recovery as therapeutic goals in patients with chronic musculoskeletal pain: two experiences with tapentadol hydrochloride

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Abstract. – OBJECTIVE: This study aimed to evaluate pain control, functioning, and quality of life (QoL) recovery in patients with chronic low back pain (cLBP) or post-traumatic osteoarthritis (OA) pain in the ankle/foot area, treated with tapentadol prolonged release and unresponsive to other treatments.

PATIENTS AND METHODS: Two observational retrospective studies were conducted using clinical practice datasets of patients with chronic pain in cLBP and OA foot/ankle at different time points (total follow-up=60-90 days). The studies assessed pain intensity by the Numerical Rating Scale (NRS) pain scale (patients were classified as responder in case of ≥30% pain reduction), QoL by the 5-level EQ-5D (EQ-5D-5L) questionnaire, patient satisfaction by the 7-point Patients' Global Impression of Change (PGIC) scale; cLBP health status by the Roland Morris Disability Questionnaire (RMDQ); foot and ankle functional status by European Foot and Ankle Society (EFAS) score; and treatment-related AEs.

RESULTS: For the cLBP setting, 37 patients were enrolled, of which 86.50% were classified as responders (n=32; CI: 75.5% ÷ 97.5%).

For the foot/ankle OA pain setting, 21 patients were enrolled. Pain assessment at final follow-up was available only for 11 patients, of which 72.73% (n=8; CI: 39.0% ÷ 94.0%) were classified as responders.

Statistically significant improvements were seen in the RMDQ, EQ-5D-5L, and PGIC scores in cLBP. Improvements in the EFAS, EQ-5D-5L, and PGIC scores were seen in OA as well. The incidence of treatment-related adverse reactions was low in both studies.

CONCLUSIONS: In the study population, tapentadol prolonged release was effective and well tolerated in treating cLBP and post-traumatic foot/ankle OA chronic pain when used in a multimodal manner. The reduction in pain was accompanied by clinically relevant improvements in patients' functionality and QoL.

Key Words:
Tapentadol, Low back pain, Osteoarthritis, Chronic pain, Opioids, Quality of life.

Introduction

Low back pain (LBP) is the most common type of musculoskeletal pain. The 2019 Global Burden of Disease Report outlines that LBP ranks 9th among the Level 3 causes of global disability-adjusted life-years (DALYs) – with a 46.9% increase in numbers of DALYs from 1990. LBP prevalence is estimated to be ~7.5% of the global population, meaning around 600 million people[1]. The proportion of people presenting to primary care with a specific identifiable cause of LBP is estimated to be 0.7-4.5% with osteoporotic vertebral fractures, 5% with inflammatory spondyloarthropathies, 0.0-0.7% with malignancy, and 0.01% with infections[2,3]. However, in most cases, LBP does not have a specific cause, and progression to a chronic state is common[4,5]. In the majority of patients, chronic LBP (cLBP) presents features of both nociceptive and neuropathic pain[6,7] and is not linked to a distinct, identifiable etiology[2,3].

Osteoarthritis (OA) and LBP can be intertwined as OA can cause LBP; indeed, many elderly patients with OA also suffer from LBP[8]. OA is a highly prevalent rheumatic musculoskeletal disorder, affecting >300 million people globally, and is considered one of the most frequent causes of chronic pain; in particular, foot/ankle OA is an increasing issue in the healthcare sector and affects around 1% of the global population[1,9-11]. Despite being less prevalent than cLBP, foot/ankle OA is nonetheless a severe and debilitating condition,

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often impairing even the ability to walk and resulting in poorer functioning, physical outcomes, and QoL[12].

Both chronic LBP and ankle OA are complex conditions with multiple contributors to both the pain and associated disability, including psychological factors, social factors, biophysical factors, comorbidities, and pain-processing mechanisms[4,10,13]. Indeed, recent advances in chronic pain as a disease state highlight its importance not only from biological and neurological perspectives but also as a psychological and social problem. Pain-related conditions such as impaired functional status, anxiety, and discomfort often complicate its treatment and negatively impact patients' quality of life (QoL), also resulting in high economic costs for society[4,13-15].

Proper control of chronic pain is crucial. As cLBP etiology is often not defintaable, cLBP treatment is mostly symptomatic. It aims to reduce pain, improve function, improve QoL, and prevent worsening of the condition, usually with a multimodal approach with pharmacological and non-pharmacological treatments[16,17]. OA management also involves a multimodal approach, including pain control[18-20]. The main goal for patients with severe chronic pain (including cLBP and post-traumatic ankle/foot OA pain) is to receive effective therapeutic options that can guarantee – beyond pain control – functional recovery and QoL improvements. Therefore, it is of paramount importance to have a treatment that can be effective and sustainable over time, with a favorable tolerability profile[4,14,18]. The European Pain Federation has recently issued clinical recommendations on chronic non-cancer pain. According to these recommendations, opioid analgesia can be considered as a treatment option for certain patients who are highly monitored. This is only if established non-pharmacological treatments or non-opioid analgesics are ineffective, contraindicated, or not tolerated[1].

The American College of Physicians also suggests that opioids should be used only when cLBP patients fail first-line treatments and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients[22]. According to recommendations on OA treatment by the Italian Rheumatology Society (although drafted for hip, knee, and hand and not specific for ankle OA), opioids can be used in case of severe pain[23]. Pharmacological treatments should always be coupled with non-pharmacological interventions to maximize outcomes[24]. In this perspective, the use of the atypical opioid tapentadol alongside other (non-pharmacological) interventions might represent an option in those selected patients in whom pain cannot be controlled with first-line, non-opioid treatment[6,25-27].

Tapentadol combines the two mechanisms of action of μ-opioid receptor agonism and noradrenaline reuptake inhibition in one molecule. This dual mechanism of action synergistically provides strong analgesia comparable to that of strong opioids such as oxycodone in a broad range of chronic nociceptive and neuropathic pain conditions[26,28,29]. However, it has a better security profile – such as favorable gastrointestinal tolerability – compared to other opioids, such as oxycodone-naloxone, morphine, hydromorphone, and oxycodone alone, even in special populations, such as the elderly, allowing a rapid titration[6,8,27,28,30].

Based on the pharmacologic rationale and solid literature clinical background[6,8,26,25,28,30-33], our Pain Center at the Orthopaedics and Traumatology Unit of the University Hospital of Perugia (Italy) developed a longtime clinical experience with tapentadol prolonged release (PR). This study aims to evaluate pain control and the recovery of functioning and QoL in tapentadol-naïve patients with severe cLBP or post-traumatic OA pain in the ankle/foot area, treated with tapentadol PR in our center.

Patients and Methods

These were two observational retrospective studies using clinical practice data. From January 2022 onwards, our center implemented a protocol for the management of chronic pain, which incorporates functionality questionnaires and follow-up visits (Table I). The analyzed data were collected between January and November 2022. The original study designs were switched from prospective to retrospective due to the COVID-19 outbreak.

Consecutive adult patients with chronic pain and treated with tapentadol PR at the Orthopedics and Traumatology Unit of the University Hospital of Perugia (Italy) with two different diagnoses, namely (1) cLBP and (2) post-traumatic foot/ankle OA pain, were enrolled in the study.

To be included in the analyses, patients had to be ≥18 years old, have a diagnosis of either severe cLBP or severe chronic foot/ankle post-traumatic

Table I. Center protocol course and treatments/assessments according to the different time points for the two patient populations.

	Chronic low back pain					Ankle/foot osteoarthritis pain				
	T0: Baseline	V1: Day 3 (phone call)	V2: Day 30	V3: Day 60	V4: Day 90	V0: Baseline	V1: Day 3	V2: Day 15	V3: Day 30	V4: Day 60
Informed consent	X					X				
Inclusion/exclusion criteria assessment	X					X				
Anamnesis, general goal exam	X					X				X
Tapentadol PR dosing	X	X	X	X	X	X	X	X	X	X
Pain intensity NRS assessment	X	X	X	X	X	X	X	X	X	X
EQ5D assessment	X	X	X	X	X	X		X		X
RMDQ assessment	X	X	X	X	X					
EFAS scale assessment						X		X		X
PGIC scale assessment			X	X	X	X		X		X
Tolerability/AEs assessment	X	X	X	X	X	X	X	X	X	X

AEs, adverse events; EFAS, European Foot and Ankle Society. PGIC, Patients' Global Impression of Change; PR, prolonged release; RMDQ, Roland Morris Disability ues-tionnaire.

OA pain lasting ≥3 months, having a severity condition in which pain affects the QoL resulting in need of treatment with a strong opioid analgesic (based on the investigators' evaluations), Numerical Rating Scale (NRS) pain intensity threshold ≥6, and tapentadol-naïve. Tapentadol (or other strong opioids) is not used in our center in case of patients with a history of drug abuse/alcoholism, malignant chronic pain syndromes, severe respiratory failure (PaO_2 <50 mmHg), untreated asthma, obstructive sleep apnea, acute pancreatitis or biliary-tract disease, paralytic ileus, inflammatory bowel disease, New York Heart Association >III, recent (<6 months) acute coronary syndrome, recent (>1 year) stroke or head injury, receiving or having received mono-amino oxidase inhibitors in the last 14 days, nursing mothers, lactose intolerance, back pathologies with a surgical indication, LBP with nerve irradiation, vertebral neoplastic lesions, renal and/or liver impairment. All patients could continue or start other (non-)pharmacological interventions such as non-analgesic medications, physiokinesitherapy, psychotherapy, corsets, etc.

Table I summarizes the usual protocol followed by our clinic. At baseline, examination for enrollment and data collection (including demographic data), general exam of the vertebral column or foot/ankle, and first tapentadol administration were carried out. Tapentadol PR was administered following the summary of product characteristics. To evaluate the onset of any adverse effects, opioid-naïve patients received a starting dose of tapentadol PR 50 mg twice/day for 3 days. After 3 days, tapentadol was up-titrated to 100 mg twice/day; the titration could proceed with an additional 50 mg twice/day every three days until an adequate analgesic effect was obtained, with a maximum daily dose of 500 mg. Patients switching from other opioids followed the standard clinical practice suggested by major guidelines, i.e., clinical individualized considerations plus the use of equianalgesic tables in order to reach an adequate analgesic effect. Some patients underwent kinesitherapy and/or used orthopedic corsets as well.

Both studies evaluated the reduction of pain intensity ≥30% on a Numerical Rating Scale (NRS) pain scale (0-10) from baseline (T0) to study completion (T4, day 60 for OA and day 90 for cLBP); patients experiencing a ≥30% reduction in pain intensity were classified as responders. Other investigations included QoL assessment measured by 5-level EQ-5D (EQ-5D-5L), patient satisfaction measured on the 7-point Patients' Global Impression of Change (PGIC) scale, assessment of treatment-related AEs inducing dropouts, health status for cLBP measured by the Roland Morris Disability Questionnaire (RMDQ), for patients with cLBP only, and foot and ankle functional status measured by European Foot and Ankle Society (EFAS) score (for patients with OA pain only). The EQ-5D-5L index value was calculated according to the EQ-5D-5L User Guide Version 3.0, September 2019, using the Italian value set reported by Finch et al[34] as weight.

The studies were approved by the local institutional review board and conducted according to the Declaration of Helsinki. All patients provided written informed consent.

Statistical Analysis

When the present studies were designed as prospective studies, we estimated to enroll 50 patients in both settings. These samples would have produced a 95% CI of the proportion of responders with a precision (width of the 95% CI) of at least 29%. Unfortunately, due to unforeseen circumstances related to the post-COVID-19 working load organization, the study designs were switched to a retrospective, and only 37 patients with cLBP and 21 with OA were eligible; nonetheless, collected data reflected the current clinical practice and were worth being analyzed.

The percentage of responders has been reported with a relative 95% CI. Inferential statistics was carried out only in the cLBP study, as the OA study enrolled a very low number of patients and had missing data. The changes in NRS pain, RMDQ and EQ-5D-5L scores at the various time points were evaluated by means of analysis of variance (ANOVA) with repeated measures considering the appropriate multiple comparisons with respect to the baseline mean. The frequency distribution of each single dimension of the EQ-5D-5L and PGIC questionnaires related to the post-baseline visits was compared *vs*. the baseline distribution using the non-parametric McNemar test. Safety analyses were carried out with descriptive statistics describing the number and percentages of patients who experienced any AEs.

All the continuous variables have been reported as means, standard deviation (SD), and median, while the discrete and nominal variables have been reported in tables with respective frequencies and percentages. All analyses were produced using SAS version 9.4 (Cary, NC, USA). Statistical significance was reached when $p<0.05$.

Results

Severe Chronic Low Back Pain

In total, 37 patients (22 males, 59.5%) with severe cLBP were enrolled in the study. Patients' characteristics and demographic data are reported in Table II. The median tapentadol PR dose was 100 mg at baseline, increasing to 200 mg at V2, 300 mg at V3, and 400 mg at V4 (maximum dose 400 mg).

86.5% (n=32; 95% CI: 75.5-97.5) of patients were classified as responders at V4. NRS pain intensity at V0 was 6.86±0.95, and it significantly decreased at all timepoints; namely, it decreased by 0.65±1.16 points at V2 (95% CI: -1.11 to -0.19; $p<0.01$), 2.19±1.14 points at V3 (95% CI: -2.65 to -1.73; $p<0.01$), and 3.14±1.53 at V4 (95% CI: -3.60 to -2.67; $p<0.01$) (Figure 1).

RMDQ scored 9.27±2.77 at V0, significantly decreasing at all time points (Figure 1), namely by 0.78±1.69 points at V2 (95% CI: -1.50 to -0.07; $p<0.05$), 2.30±1.85 points at V3 (95% CI: -3.01 to -1.58; $p<0.01$), and 4.11±2.75 at V4 (95% CI: -4.82 to -3.39; $p<0.01$).

Regarding QoL, EQ-5D-5L scores significantly improved (n=37, Table III and Figure 2). At baseline, EQ-5D-5L VAS score was 60.81±22.84, improving by 1.22±16.30 points at V2 and by 3.39±19.15 at V3 (differences were not significant); statistical significance was reached at V4, where scores improved by 9.19±18.85 points (95% CI: 2.62-15.76; $p<0.01$). At baseline, EQ-5D-5L index score was 0.56±0.23, and it significantly increased by 0.12±0.18 points at V2 (95% CI: 0.05-0.18; $p<0.01$), 0.23±0.19 points at V3 (95% CI: 0.17-0.30; $p<0.01$), and 0.33±0.33 points at V4 (95% CI: 0.26-0.39; $p<0.01$). Most improved domains comprised pain/discomfort, activities, mobility, and self-care, whilst anxiety/depression scores did not change significantly (Table III).

According to PGIC scores, the vast majority of patients reported subjective improvements at V4.

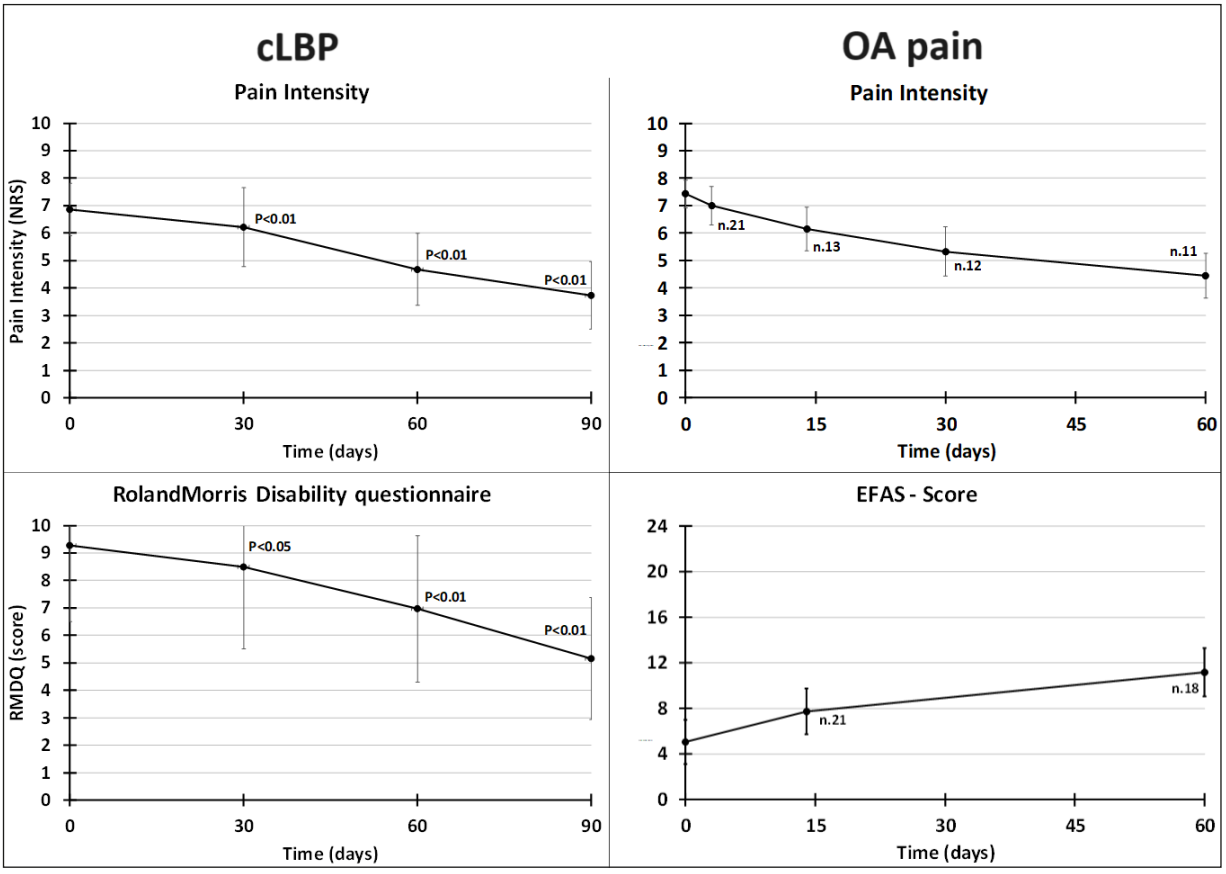

Figure 1. Pain intensity as measured by the NRS pain scale (top panels) and functional improvements in cLBP as measured by the RMDQ (bottom, left) and in OA pain as measured by the EFAS scores (bottom, right) at different time points. cLBP, chronic low back pain; EFAS, European Foot and Ankle Society; OA, osteoarthritis; RMDQ, Roland-Morris disability questionnaire.

Table II. Patients' characteristics and demographic data.

Patients' characteristics and demographic	cLBP (n=37)	OA pain (n=21)
Mean age, years (SD)	60.4 (13.0)	50.9 (11.6)
Female, n (%)	15 (40.5)	9 (42.9)
Male, n (%)	22 (59.5)	13 (61.9)
BMI, kg/m^2 (SD)	25.5 (5.9)	25.4 (3.1)
Mean years since pain onset (SD)	3.2 (3.7)	3.09 (5.22)
Previous analgesic therapies, n (%)		
None	3 (8.1)	9 (42.9)
1	14 (37.8)	2 (9.5)
2 or more	20 (54.1)	10 (47.6)
Buprenorphine	3 (8.1)	–
Codeine	1 (2.7)	–
Coefferalgan	2 (5.4)	–
Cortisone	1 (2.7)	–
Diclofenac	1 (2.7)	–
FANS	17 (45.9)	11 (52.4)
Oxycodone/Naloxone	3 (8.1)	3 (14.3)
Paracetamol	25 (67.6)	7 (33.3)
Paracetamol + codeine	2 (5.4)	–
Tramadol	7 (18.9)	2 (9.5)
Pregabalin	–	1 (4.8)
Opioids	–	1 (4.8)
Physiokinesitherapy	–	1 (4.8)
Others	2 (5.4)	–
Tolerability of previous antalgic therapies, n (%)		
N/A	1 (2.7)	13 (61.9)
Very bad	1 (2.7)	0 (0.0)
Poor	1 (2.7)	0 (0.0)
Good	6 (16.2)	5 (23.8)
Very good	28 (75.7)	3 (14.3)

BMI, body mass index; cLBP, chronic low back pain; OA, osteoarthritis; –, not available.

The proportion of patients reporting "Moderately better and a slight, but noticeable change" or higher increased from 21.6% (n=8) at V2 to 64.8% (n=24) at V3 and up to 91.9% (n=34) at V4. The reported impressions of noticeable improvements were statistically significant at V3 and remained so at V4 ($p<0.01$ for both; Table IV).

At V4, 21.6% (8/37) of patients reported at least one treatment-emergent AE, of which all were judged as related to treatment with tapentadol PR. At V4, no AE was reported as serious, and 94.6% (35/37) of patients reported good/very good judgment about treatment tolerability. The most common treatment-emergent AE were dizziness (n=6, 16.2%), nausea (n=4, 10.8%), headache (n=2, 5.4%), vomiting (n=2, 5.4%), and drowsiness (n=1, 2.7%). No patients interrupted the treatment due to AEs or tolerability issues.

OA PAIN in the Foot/Ankle Area

In total, 21 patients with OA pain in the foot/ankle area were enrolled in the study. Patients' characteristics and demographic data are reported in Table II. The median tapentadol PR dose was 100 mg at baseline and V1, increasing to 200 mg at V2, V3 and V4 (maximum dose 300 mg). Due to the low number of patients involved, only descriptive statistics were carried out in the OA setting.

Pain assessment at V4 was available only for 11 patients due to COVID-related reasons. Eight out of the 11 available patients (72.7%) experienced a >30% reduction in NRS scores. NRS pain intensity at baseline was 7.43±0.51, decreasing by 1.10±0.74 points at V2 (n=12), by 2.20±0.79 points at V3 (n=12), and by 2.90±0.74 points at V4 (n=11) (Figure 1).

Table III. EQ-5D-L5 scores at different time points.

	cLBP				OA pain		
	V0	V2	V3	V4	V0	V2	V4
Mobility							
n	37	37	37	37	21	21	19
I have no problems walking about	25 (67.6)	29 (78.4)	33 (89.2)	35 (94.6)	0 0.0)	0 (0.0)	0 (0.0)
I have slight problems in walking about	7 (18.9)	4 (10.8)	2 (5.4)	2 (5.4)	0 (0.0)	2 (9.5)	16 (76.2)
I have moderate problems in walking about	4 (10.8)	3 (8.1)	2 (5.4)	0 (0.0)	11 (52.4)	18 (85.7)	3 (14.3)
I have severe problems in walking about	1 (2.7)	1 (2.7)	0 (0.0)	0 (0.0)	10 (47.6)	1 (4.8)	0 (0.0)
I am unable to walk about	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p-value*	–	0.2615	0.0293	0.0117	–	–	–
Self-Care							
n	37	37	37	37	21	21	19
I have no problems washing or dressing myself	22 (59.5)	26 (70.3)	27 (73.0)	32 (86.5)	8 (38.1)	10 (47.6)	16 (76.2)
I have slight problems washing or dressing myself	8 (21.6)	8 (21.6)	8 (21.6)	5 (13.5)	6 (28.6)	7 (33.3)	3 (14.3)
I have moderate problems washing or dressing myself	6 (16.2)	2 (5.4)	2 (5.4)	0 (0.0)	7 (33.3)	4 (19.0)	0 (0.0)
I have severe problems washing or dressing myself	1 (2.7)	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
I am unable to wash or dress myself	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p-value*	–	0.1520	0.1546	0.0215	–	–	–
Activities							
n	37	37	37	37	21	21	18
I have no problems doing my usual activities	0 (0.0)	8 (21.6)	10 (27.0)	21 (56.8)	0 (0.0)	0 (0.0)	0 (0.0)
I have slight problems doing my usual activities	10 (27.0)	14 (37.8)	12 (32.4)	12 (32.4)	0 (0.0)	4 (19.0)	12 (57.1)
I have moderate problems doing my usual activities	18 (48.6)	9 (24.3)	13 (35.1)	4 (10.8)	9 (42.9)	14 (66.7)	4 (19.0)
I have severe problems doing my usual activities	9 (24.3)	6 (16.2)	2 (5.4)	0 (0.0)	12 (57.1)	3 (14.3)	2 (9.5)
I am unable to do my usual activities	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p-value*	–	0.0348	0.0001	<0.0001	–	–	–
Pain/Discomfort							
n	37	37	37	37	21	21	18
I have no pain or discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
I have slight pain or discomfort	0 (0.0)	0 (0.0)	4 (10.8)	14 (37.8)	0 (0.0)	1 (4.8)	10 (47.6)
I have moderate pain or discomfort	11 (29.7)	21 (56.8)	27 (73.0)	22 (59.5)	4 (19.0)	17 (81.0)	8 (38.1)
I have severe pain or discomfort	22 (59.5)	13 (35.1)	5 (13.5)	1 (2.7)	16 (76.2)	3 (14.3)	0 (0.0)
I have extreme pain or discomfort	4 (10.8)	3 (8.1)	1 (2.7)	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)
p-value*	–	0.0067	0.0003	<0.0001	–	–	–

Table continued

Table III *(Continued)*. EQ-5D-L5 scores at different time points.

	cLBP				OA pain		
	V0	V2	V3	V4	V0	V2	V4
Anxiety/Depression							
n	37	37	37	37	21	21	19
I am not anxious or depressed	31 (83.8)	32 (86.5)	32 (86.5)	34 (91.9)	8 (38.1)	7 (33.3)	6 (28.6)
I am slightly anxious or depressed	2 (5.4)	2 (5.4)	3 (8.1)	2 (5.4)	4 (19.0)	4 (19.0)	3 (14.3)
I am moderately anxious or depressed	4 (10.8)	3 (8.1)	2 (5.4)	1 (2.7)	6 (28.6)	7 (33.3)	10 (47.6)
I am severely anxious or depressed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (14.3)	3 (14.3)	0 (0.0)
I am extremely anxious or depressed	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
p-value*	–	0.3173	0.3679	0.2615	–	0.5724	0.3062
Health impression							
n	37	37	37	37	21	21	19
How good or bad your health is today, VAS mean score (sd)	60.81 (22.84)	62.03 (25.40)	64.19 (23.73)	70.00 (20.00)	39.29 (7.79)	52.38 (9.17)	66.67 (6.18)
p-value#	–	0.7145	0.3106	0.0066	–	–	–
Index value, mean score (sd)	0.56 (0.23)	0.67 (0.26)	0.79 (0.17)	0.88 (0.08)	0.27 (0.27)	0.60 (0.20)	0.74 (0.09)
p-value#	–	0.0005	<0.0001	<0.0001	–	–	–

Data are reported as n (%). **p*-value is based on the McNemar test compared to the baseline visits *vs.* post-baseline visits. #*p*-value is based on the Least Significance Difference *t*-test calculated on ANOVA error values. cLBP, chronic low back pain; OA, osteoarthritis.

EFAS assessment was available at V2 and V4, showing improvements (Figure 1). The baseline EFAS score was 5.05±1.94, and it increased by 2.61±2.17 and 6.17±2.31 points at V2 (n=21) and V4 (n=18), respectively. The baseline EFAS Sport score was 0.62±1.26 (n=13), and it increased by 0.64±0.92 and 3.82±2.56 points at V2 (n=14) and V4 (n=13), respectively. The EFAS Sport score was assessed only in individuals who practiced sports or were seeking the return to physical activities during the study period, hence the lower number of patients assessed compared to the EFAS score.

Regarding QoL, EQ-5D-5L scores also show improvements (Table III and Figure 2). VAS score was 39.29±7.79 at baseline, increasing by 11.67±7.48 and 26.67±8.04 points at V2 (n=21) and V4 (n=18), respectively. The index value was 0.27 during the baseline visit, and it increased by 0.32±0.24 and 0.44±0.22 points at V2 and V4, respectively (n=19 for both). Most improved domains comprised pain/discomfort, activities, mobility, and self-care, while anxiety/depression did not change (Table III).

According to PGIC scores, 88.9% (16/18) of patients reported noticeable changes at V4 (Table IV), and 94% (17/18) of patients improved their valuation.

At V4, 31 AEs were registered. Eight (38.1%) patients did not experience any AE, 5 (23.8%) experienced one, and nine (42.9%) experienced two or more. The most common AEs were nausea (n=12, 57.1%), drowsiness (n=6, 28.6%), and dizziness (n=2, 9.5%). No patient's treatment was interrupted due to AEs or tolerability issues.

Discussion

In these studies, we report on patients diagnosed with severe cLBP or severe foot/ankle traumatic OA pain and treated with tapentadol PR at the Orthopedics and Traumatology Unit of the University Hospital of Perugia (Italy). Although the study was retrospective and enrolled a low number of patients, the use of validated scales (NRS, RMDQ, EFAS score, and EQ-5D-L5) allowed the yield of standardized, comparable data.

Table IV. PGIC answer distribution at different timepoints.

PGIC answers	cLBP			OA pain	
	V2 (n=37)	V3 (n=37)	V4 (n=37)	V2 (n=21)	V4 (n=18)
No change (or condition has got worse)	20 (54.1)	2 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)
Almost the same, hardly any change at all	4 (10.8)	3 (8.1)	2 (5.4)	5 (23.8)	0 (0.0)
A little better, but no noticeable change	4 (10.8)	6 (16.2)	1 (2.7)	9 (42.9)	2 (11.1)
Somewhat better, but the change has not made any real difference	1 (2.7)	2 (5.4)	0 (0.0)	4 (19.0)	3 (16.7)
Moderately better and a slight but noticeable change	8 (21.6)	15 (40.5)	12 (32.4)	2 (9.5)	7 (38.9)
Better and definite improvement that has made a real and worthwhile difference	0 (0.0)	8 (21.6)	15 (40.5)	1 (4.8)	5 (27.8)
A great deal better and a considerable improvement that has made all the difference	0 (0.0)	1 (2.7)	7 (18.9)	0 (0.0)	1 (5.6)
p-value*	–	0.0081	0.0010	–	N/A

Data are reported as n (%). **p*-value is based on the McNemar test comparing V2 *vs.* V3 and V4. cLBP, chronic low back pain; OA, osteoarthritis; PGIC, Patients' Global Impression of Change.

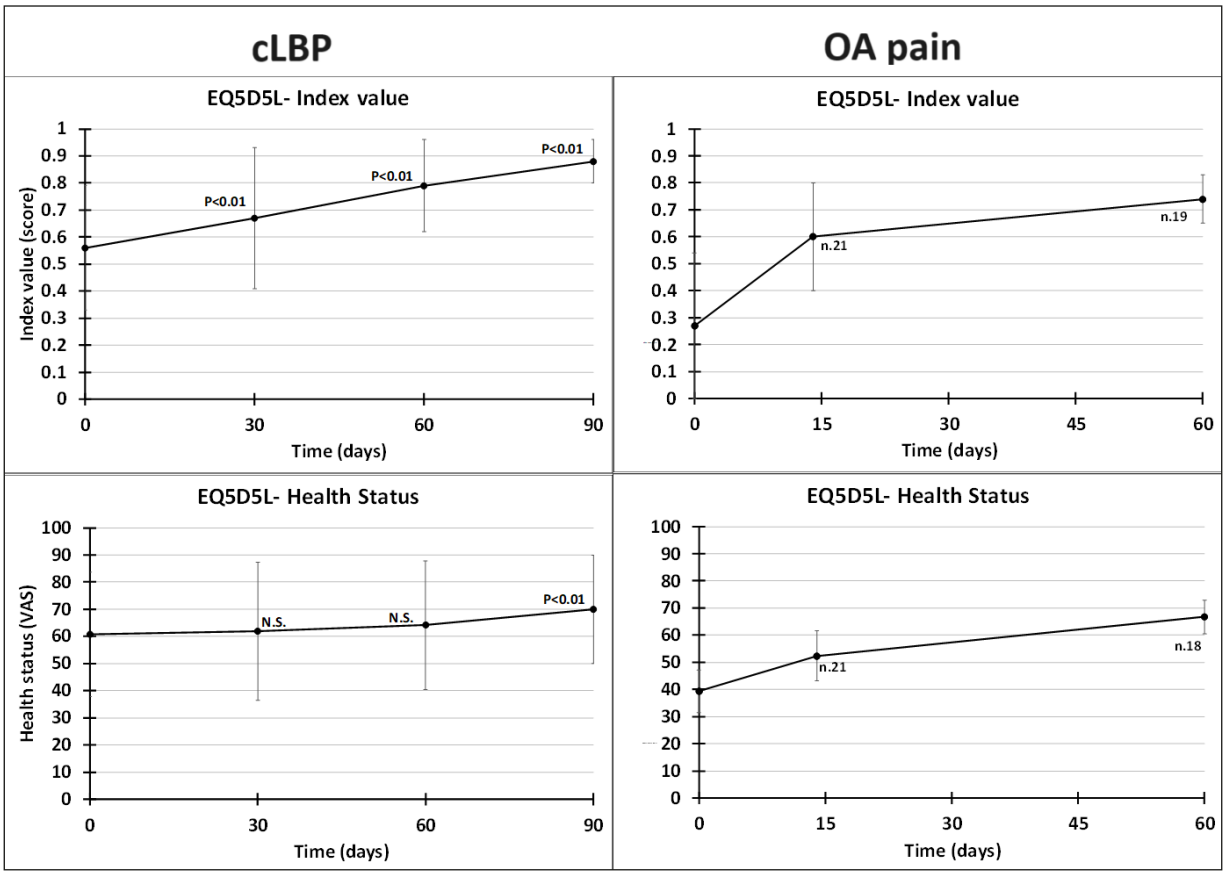

Figure 2. EQ-5D-5L index and VAS scores at different time points. Improvements in the EQ-5D-5L reflect improvements in the patient's quality of life. cLBP, chronic low back pain; OA, osteoarthritis; VAS, visual analogue scale.

The RMDQ is a health status measure designed to be completed by patients to assess physical disability due to LBP[35]; the EFAS score is a patient-reported outcome measure specifically designed for the foot and ankle and consisting of six questions on pain and function[36]; the EQ-5D-5L

questionnaire captures multidimensional aspects of health-related QoL, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[37].

As all enrolled patients discontinued their previous pharmacological therapy, benefits are attributable to tapentadol PR with or without non-pharmacological intervention (such as physiokinesitherapy) in those patients who undertook them. This is of pivotal importance as pharmacological and non-pharmacological interventions are not mutually exclusive and must be part of a comprehensive clinical practice that targets chronic pain with a multimodal approach[4,13-15,24,38-42].

Our experiences showed that tapentadol PR treatment resulted in consistent and sustained pain relief after 60-90 days of treatment for most patients. The decrease in NRS pain scores reflects a clinically important reduction in pain intensity, and statistically significant pain relief was already achieved after 15-30 days of treatment. On average, pain decreased from severe (NRS score –7) to moderate (NRS score –4), allowing functional and QoL recovery (Figure 1). The majority of patients, especially those with cLBP, experienced a pain reduction of at least 30% on the pain NRS, representing a substantial clinical improvement[43]. Significant pain and discomfort reductions were also captured by the EQ-5D-L5 questionnaire (Figure 2). This is of added relevance if we consider that the severity of the patient's pain condition (intensity, disability, poor QoL), on top of its long-lasting duration (more than 3 years), was particularly challenging. Indeed, randomized trials and observational studies found tapentadol PR to be more effective than other commonly used, strong opioids (e.g., morphine, hydromorphone, oxycodone ± naloxone) in treating cLBP, especially in patients with an additional neuropathic component – present in over three-quarters of cLBP patients[6,30,44,45]. This is probably thanks to its dual mechanism of action, which also acts on descending noradrenergic pathways, contributing to the reduction in neuropathic pain dimensions[46,47].

Assessment of patients' functionality and QoL using the RMDQ, the EFAS score, and the EQ-5D-5L questionnaire provided valuable insights into the impact of tapentadol PR on functional status and daily life improvements. Functionality or functional status is defined as the ability to ambulate, function cognitively, return to work, and complete daily activities, as well as the absence of mood or sleep disturbances[48,49]. Indeed, the domains of "physical functioning", "pain intensity" and "QoL" are considered equally important outcome measures in chronic pain studies[39,40]. Actually, individual autonomy and the ability to perform daily activities through improvements of functioning are far more important than complete pain resolution for patients and healthcare professionals[38,50,51]. In chronic pain studies, it is pivotal to assess these domains beyond pain reductions, as reducing pain does not necessarily result in improved physical health, and the correlations between changes in pain intensity and physical disability tend to be modest[52,53]. Studies in patients with cLBP and OA have shown tapentadol PR to be effective in improving all dimensions of QoL (often to a greater extent than oxycodone ± naloxone[30,49]), with improvements being associated with marked functional recovery and improved sleep quality[26,30,32,33]. In our studies, several patients reported major impairments, such as severe problems in walking about and carrying out usual activities at baseline; the statistically significant improvements in RMDQ, EFAS and EQ-5D-5L scores indicate enhanced functional ability and recovery among treated patients. This suggests that tapentadol PR not only provided pain relief but also contributed to the restoration of patient's functional capabilities and a notable improvement in patients' overall well-being. By effectively addressing pain and reducing the burden of discomfort, tapentadol PR, with or without non-pharmacological treatments, may enable selected patients to participate better in daily activities, enhance their physical functioning, and ultimately lead to an improved QoL. Despite the fact that a significant reduction in pain might lead to a general state of well-being perceived as very satisfactory by the patient, allowing the recovery of physical abilities necessary to face most of the common activities of daily life, this relationship is not always straightforward[52,53]. Thus, these findings support the notion that tapentadol PR can contribute to improved functionality, QoL, and may have a meaningful impact on patients' ability to engage in daily activities and tasks beyond simple pain control.

In addition to pain reduction and improvements in functionality, our study also assessed the impact of tapentadol PR on treatment satisfaction using the PGIC scale. Overall, the reduction of pain and subsequent amelioration of patients' functionality and QoL were reflected by the PGIC scale score, where almost all patients of both groups reported noticeable changes and improved their evaluation.

Moreover, in our experience, we provided an initial therapy of 50 mg twice daily, as indicated in the Summary of Product Characteristics[54]; dosage could be increased with an additional 50 mg twice/day until proper pain control was achieved. Data from observational studies[45] of clinical practice show mean daily tapentadol PR doses between 192 and 287 mg. In our case, median doses were higher (400 mg and 200 mg at study termination for cLBP and OA patients, respectively) but well below the maximum recommended dose of 500 mg (which was never reached in either group) and comparable to those used in RCTs (200-380 mg)[45].

The most common treatment-related AEs in our study were nausea, drowsiness, and dizziness. AE number was low, and almost all cLBP patients judged tolerability to be either good or very good. The synergistic action of the noradrenaline reuptake inhibition allows for a reduced μ-opioid load[55], resulting in a lower number of Aes, such as nausea, vomiting, and constipation, which are typical AEs of other opioids, such as oxycodone±naloxone, morphine, and hydromorphone[6,45]. No patients of both groups stopped treatment due to safety concerns, suggesting that tapentadol has a good tolerability profile. This is in line with literature data and meta-analyses where tapentadol PR consistently showed better tolerability (lowest incidence of overall AEs) and lowest trial withdrawal rate compared to the above opioids[6,30,45].

Limitations

The reported studies have several limitations. They were designed as prospective but switched to retrospective due to COVID-19-related reasons; this also resulted in missing data from several patients in the OA setting, hindering statistical comparisons and data robustness. Being observational studies describing clinical practice, they have no control group and were conducted on a low number of patients, possibly chosen under a selection bias.

Measurement of pain intensity at baseline was hindered due to the absence of previous analgesic wash-out, which can be carried out in randomized trials but cannot be achieved in real-life practice due to the patient's need to be given proper treatment. Compliance was not measured, but treatment effectiveness and patients' satisfaction measured by PGIC scores suggest that patients were probably compliant overall. Concomitant interventions, such as physiokinesitherapy, psychotherapy, corsets, medications other than analgesics, etc. were not captured. Thus, the contribution to pain reduction and functionality and QoL improvements cannot be attributed to tapentadol PR alone. Indeed, as already highlighted, pharmacological and non-pharmacological interventions do not exclude each other[24,38]. In this perspective, tapentadol PR is an effective tool in the vast armamentarium needed to tackle severe chronic pain comprehensively.

Finally, considering the chronicity (i.e., duration >3 months) of the conditions studied, the follow-ups might not have been long enough to capture further or late pain improvement trends, especially in the case of OA pain (60-day follow-up).

Conclusions

Our study adds to the body of clinical and research evidence showing the positive effects of tapentadol PR in treating severe chronic pain – namely cLBP and post-traumatic foot/ankle OA pain – when used in a multimodal, comprehensive manner. In the studied population, the reduction in pain was accompanied by important improvements in patients' functionality and QoL as measured by specific, validated scales. Finally, tapentadol PR was well tolerated, with no serious AEs or treatment discontinuations.

Conflict of Interest

The authors have received financial research support (statistical analyses, medical writing, editorial assistance, and payment of the open access fees) from Grunenthal Italia Srl, and report no other confilct of interest related to this work.

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Availability of Data and Materials

Additional data will be available from the corresponding author upon reasonable request.

Authors' Contribution

Study conception and design: GR, PC, GA, AC; collection and interpretation of data: GR, PC, GA, AC; statistical analysis: Fabio Bravi; manuscript drafting: Fabio Perversi (medical writer); manuscript editing: GR, PC, GA, AC; approval to submit: GR, PC, GA, AC.

Ethics Approval

The studies were approved on February 22nd, 2023, by the "Comitato Etico Regionale dell'Umbria" (approval acceptance number: 4495/23 for the OA study and 4496/23 for the cLBP study). The studies were conducted according to the Declaration of Helsinki.

Informed Consent

All patients provided written informed consent.

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